REMARKS/ARGUMENTS

Status of the Application

In the August 8, 2007, Final Office Action, claims 26 and 29-40 were rejected. In the present response, claim 26 was amended to recite at least 95% sequence identity. Claim 29 was canceled without prejudice to or disclaimer of the subject matter recited therein. Thus, claims 26 and 30-40 are pending.

No new search is required since Applicants have increased the percentage identity to the nucleotide sequence of interest, thus the entry of the Amendment is kindly requested. No new matter was added.

Inventorship

Applicants submit herewith a Request to Correct Inventorship Under 37 C.F.R. § 1.48(b). Appropriate correction is requested.

Rejections Under 35 U.S.C. § 101

Claims 26 and 29-40 were rejected under 35 U.S.C. § 101 as not being supported by either a specific and/or substantial assorted utility or a well-established utility.

For an invention to have utility, "at least one specific, substantial, and credible utility" must be either disclosed in the specification or well-established for the invention. Utility Examination Guidelines, 66 Fed. Reg. 1092, 1094 (Jan. 5, 2001). Based upon this standard, Applicants respectfully submit that the present rejection under 35 U.S.C. § 101 for lack of utility is improper because at least one specific, substantial, and credible utility for the present application was asserted or is well-established. The standard for utility is low one, with the MPEP asserting that any utility beyond "'throw-away,' 'insubstantial,' or 'nonspecific' utilities, such as the use of a complex invention as landfill, as a way of satisfying the utility requirement of 35 U.S.C. 101" is sufficient. MPEP § 2107(II)(B)(1)(i). The instant disclosure fulfills this low standard as here, the Applicants have asserted diacylglycerol acyltransferase (DGAT) activity as a utility of the present invention (see below).

The Office rejected the claims as lacking this asserted utility. "To properly reject a claimed invention under 35 U.S.C. 101, the Office must (A) make a *prima facie* showing that the claimed invention lacks utility, and (B) provide a sufficient

evidentiary basis for factual assumptions relied upon in establishing the *prima facie* showing." MPEP § 2107.02(IV) (citing *In re Gaubert*, 524 F.2d 1222, 1224 (CCPA 1975)). Applicants respectfully submit that the Examiner's evidence fails to establish a *prima facie* case of lack of utility. The Examiner's evidence consists of citations of (1) irrelevant journal articles and (2) an incorrect conclusion that Applicants failed to provide an assay for determining DGAT activity. Regarding the journal articles, several of these references relate to the dangers of relying on sequence comparisons for determining the activity of a protein. December 18, 2006, Non-Final Office Action, at 3-4 (*hereinafter* "NF Office Action"). First, novel gene sequences routinely have their function identified correctly by sequence comparison. Second, the USPTO uses sequence homology to search the prior art. Third, in the particular case of DGAT, four "putative" DGAT protein, from human, Arabidopsis, soybean, and wheat, were subsequently shown to all have the expected DGAT activity. Consequently, for Applicants' protein of interest, the validity of sequence comparison has been documented.

The remaining references cited in the NF Office Action relate to determining activity of enzymes that modify fatty acids based on sequence identity to known proteins. NF Office Action, at 4-5. The cited references, however, do not relate to determining DGAT activity from previously known sequences, and the Examiner provides no evidence that the difficulties set forth in those references are applicable to DGATs.

Regarding the second basis of the Examiner's utility rejection, the Examiner stated that "the specification does not provide any additional information, such as an enzyme assay, to establish the utility of the claimed sequences." *Id.* at 3 (emphasis added). Applicants, however, provided in Example 8 a citation to a journal article containing a DGAT assay, Andersson *et al.*, J. Lipid. Res. 35:535-45 (1994). The assay in Andersson *et al.* was developed to assay DGAT purified from rat livers. Briefly, rat livers are isolated, homogenized and microsomes are purified. Microsomes are then treated with detergent, sonication and filtration to obtain enzyme preparations. 1,2-Dioleoyl-sn-glycerol and radioactively-labeled palmitoyl-CoA are used as substrates. The triacylglycerol product is purified by thin-layer chromatography, and the amount is measured by use of a liquid scintillator. It is well-established that an applicant need not disclose that which is known in the art. *In*

re Buchner, 929 F.2d 660, 661 (Fed. Cir. 1991). Applicants' citation of this reference in the specification should thus be sufficient evidence of a well-established utility, that is DGAT activity, and therefore the Examiner's failure to establish a *prima facie* case of lack of utility.

Even if the Examiner established a *prima facie* case of lack of utility, Applicants provided sufficient evidence showing that the asserted utility is substantial specific, and credible. If an examiner meets his burden of establishing a *prima facie* case of lack of utility, "the burden of coming forward with evidence or argument shifts to the applicant. . . . After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992); *see also In re Langer*, 503 F.2d 1380, 1391-92 (CCPA 1974) ("Assuming that sufficient reason to question the statement and its scope does exist, a rejection for lack of utility under § 101 will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the statement of utility and its scope as found in the specification are true.").[1] The utility requirement for inventions relating to nucleic acid sequences can be satisfied by basing an asserted use "upon homology to existing nucleic acids or proteins having an accepted utility." Utility Examination Guidelines, 66 Fed. Reg. 1092, 1096 cmt. 19 (Jan. 5, 2001).

> When a class of proteins is defined such that the members share a specific, substantial, and credible utility, the reasonable assignment of a new protein to the class of sufficiently conserved proteins would impute the same specific, substantial, and credible utility to the assigned protein. If the preponderance of the evidence of record, or of sound scientific reasoning, casts doubt upon such an asserted utility, the examiner should reject the claim for lack of utility under 35 U.S.C. 101. For example, where a class of proteins is defined by common structural features, but evidence shows that the members of the class do not share a specific, substantial functional attribute or utility, despite having structural features in common, membership in the class may not impute a specific, substantial, and credible utility to a new member of the class.

[1] Under a preponderance of the evidence standard, "evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true." MPEP § 2107.02(VII) (emphasis in original).

Id. As detailed below, Applicants' evidence demonstrates, by at least a preponderance of the evidence, that the DGAT activity of the claimed sequences is a substantial, specific, and credible utility.

Substantial Utility

Applicants' evidence establishes that DGAT activity is a "substantial" activity. "Courts have used the labels 'practical utility' and 'real world' utility interchangeably in determining whether an invention offers 'substantial' utility." *In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005). "'Practical utility' is a shorthand way of attributing 'real-world' value to claimed subject matter. In other words, one skilled in the art can use a claimed discovery in a manner which provides some immediate benefit to the public." *Nelson v. Bolwer*, 626 F.2d 853, 856 (CCPA 1980). As noted in the specification, "DGAT plays a fundamental role in the metabolism of glycerolipids" (page 1, line 15). Further, "DGAT is important for the generation of seed oils . . ." (page 1, line 21). The product of the DGAT reaction is triacylglycerol, and "[i]n eukayotic cells triacylglycerols are quantitatively the most important storage form of energy" (page 1, lines 11-12).

Further, Applicants note that DGAT activity does not fall into the categories of situations requiring further research to establish a substantial utility. The MPEP sets forth the following examples of insubstantial utilities:

> (A) Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved; (B) A method of treating an unspecified disease or condition; (C) A method of assaying for or identifying a material that itself has no specific and/or substantial utility; (D) A method of making a material that itself has no specific, substantial, and credible utility; and (E) A claim to an intermediate product for use in making a final product that has no specific, substantial and credible utility.

MPEP § 2107.01(I)(B) (emphasis in original). DGAT activity is not a study of the basic properties of the claimed sequences; it is not a method of treating an unspecified disease; it is not a method of identifying another material; it is not method of making a material; and it is not an intermediate product. While not being in one of these examples is not conclusive evidence of substantial utility, Applicants believe that DGAT activity is so far removed from the insubstantial nature of these

examples to question how the Examiner can consider DGAT activity to be insubstantial.

Specific Utility

Applicants' asserted utility is "specific". "A 'specific utility' is specific to the subject matter claimed and can 'provide a well-defined and particular benefit to the public.'" *Id.* § 2107.01(I)(A) (quoting *Fisher*, 421 F.3d at 1371 (emphasis in original)). For the "specific" utility requirement, "an application must disclose a use which is not so vague as to be meaningless." *Fisher*, 421 F.3d at 1371. DGAT activity is specific because it is enzymatic activity for the conversion of specific substrates, fatty acyl CoA and diacylglycerol, to specific products, triacylglycerols. Benefits to the public of DGAT activity include, for example, increasing the oil content of oilseeds when DGAT activity is overexpressed and diversion of carbon into other metabolites when DGAT activity is suppressed (page 1, lines 21-23). Further, DGAT activity cannot be called "vague",[2] as the nature of the reaction converting diacylglycerols to triacylglycerols (EC 2.3.1.20) has been known for quite some time. *See, e.g.*, Coleman & Bell "Triacylglycerol Synthesis in Isolated Fat Cells: Studies on the Microsomal Diacylglycerol Acyltransferase Activity Using Ethanol-Dispersed Diacylglycerols" 1976 J Biol Chem 251:4537-4543, attached herewith and cited in a Supplemental IDS.

Credible Utility

Finally, Applicant's asserted utility is credible. "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record (e.g., test data, affidavits or declarations from experts in the art, patents or printed publications) that is probative of the applicant's assertions." MPEP § 2107(II)(B)(1)(ii). "An applicant need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement." *Id.*

[2] According to Merriam-Webster's Dictionary, the definition of "vague" that appears to be most relevant here is "not clearly defined, grasped, or understood." *See* Merriam-Webster's Online Dictionary, at http://www.m-w.com/cgi-bin/dictionary?book=Dictionary&va=vague (last visited Oct. 7, 2007).

The thrust of the Examiner's attack on the utility of the present invention appears to be directed at the credibility requirement. For example, the Examiner questions Applicants' assertion of DGAT activity based on sequence homology to other known DGATs and questions Applicants' 132 Declaration filed on May 17, 2007 (*hereinafter* "Declaration") as being based on a DGAT assay from a post-filing reference. August 8, 2007, Final Office Action, at 3 (*hereinafter* "Final Office Action"). The Examiner's questioning of Applicants' assertions and data is flawed, however, because while "an asserted use must show that that [sic] claimed invention has a significant and presently available benefit to the public," *Fisher*, 421 F.3d at 1371, an applicant can overcome a utility rejection "by suitable proofs indicating that the statement of utility and its scope as found in the specification are true." *Langer*, 503 F.2d at 1391-92 (emphasis added). Evidence submitted to confirm a fact found in the specification as filed can include "after-filed" information. *See, e.g., In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995) (finding that a declaration "dated after applicants' filing date, can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification. It does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed (i.e., demonstrated utility)."). Here, the data described in the Declaration was produced using a journal article published post-filing, but such data was submitted only to confirm a fact found in the specification as filed, namely, that the claimed invention has DGAT activity. Thus, the only review that the Examiner should have undertaken was whether the asserted DGAT activity was credible, that is, whether the "the reliability of the statement based on the logic and facts that are offered by the applicant [supported] the assertion of utility." MPEP § 2107.02(III)(B).

Applicants' Declaration demonstrates that the asserted utility is credible. As described in Applicants' Declaration, the soybean protein encoded by cDNA clone sr1.pk008.a8 and the wheat protein encoded by cDNA clone wr1.pk0119.b6:fis were expressed in the yeast *Sacharomyces cerevisiae*. The yeast strain used was a mutant strain in which the DGAT gene, DGA1, and the PDAT gene, LRO1, had been deleted. Microsomal fractions were prepared from the transgenic yeast lines, and DGAT assays were performed using radioactively-labeled oleoyl-CoA and endogenous diacylglycerol. Triacylglycerol (TAG) was isolated by thin-layer

chromatography and TAG was measured using liquid scintillation counting. The protein preparation from yeast transformed with the soybean gene produced 868 +/- 25 units of activity (pmol of TAG/min/mg of microsomal protein), the protein preparation from yeast transformed with the wheat gene produced 521 +/- 7 units of activity and the protein preparation from yeast transformed with the vector control produced 21 +/- 10 units of activity. Consequently, the soybean protein encoded by sr1.pk008.a8 and the wheat protein encoded by cDNA clone wr1.pk0119.b6:fis were each shown to have DGAT activity.

Further, the showing of DGAT activity for only one species of the claimed genus is sufficient because the claimed sequences are related by 95% sequence identity. "Where an applicant has established utility for a species that falls within an identified genus of compounds, and presents a generic claim covering the genus, as a general matter, that claim should be treated as being sufficient under 35 U.S.C. 101." MPEP § 2107.02; *see also Brana*, 51 F.3d at 1567 ("[E]vidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility."). Here, the Declaration demonstrates DGAT activity for one of the species within claim 26, a sequence having one amino acid difference from SEQ ID NO:16. Declaration at 3-4. In accordance with MPEP § 2107.02, Applicants' data should be sufficient for the entire claimed genus.

From the facts of the present case, the only reasonable conclusion is that Applicants' statement of asserted utility is credible. Applicants' use of a test from a well-respected journal (The Journal of Biological Chemistry) and the conclusiveness of the results in the Declaration should have convincingly established to the Examiner the credibility of the asserted utility. Further, Applicants remind the Examiner that office personnel

> must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. Similarly, Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered.

MPEP § 2107(II). As noted above, the Examiner's countervailing evidence of lack of utility is weak at best, and is certainly not enough to tip the scale of preponderance

of evidence towards lack of utility. Further, disregarding the Declaration because it involved a test for DGAT activity developed post-filing was clear error, and, in any event, does nothing to refute the facts presented in the Declaration, namely that SEQ ID NO:16 has DGAT activity as stated in the specification as filed.

In light of the above, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 101.

Rejections Under 35 U.S.C. § 112, 1st Paragraph

Written Description

Claims 26-40 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

Currently amended claim 26 is drawn to an isolated polynucleotide encoding a polypeptide having DGAT activity and at least 95% sequence identity to SEQ ID NO:16. Dependent claims 30-40 also require the isolated polynucleotide to encode a polypeptide having DGAT activity.

Applicants' claimed invention substantially conforms to Example 14 of the "Synopsis of Application of Written Description Guidelines" (66 Fed. Reg. 1099 (Jan. 5, 2001), *available at* http://www.uspto.gov/web/menu/written.pdf (last visited October 5, 2007) (*hereinafter* "Written Description Guidelines"). In Example 14 of the Written Description Guidelines, the exemplary claim is directed to "A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B." Written Description Guidelines, at 53. Included in the Example 14 specification is an "indicat[ions] that procedures for making proteins with substitutions, deletions, insertions and additions is routine in the art and . . . an assay for detecting the catalytic activity of the protein." *Id.* Under the "Analysis" section of Example 14, the requirements of 95% identity to SEQ ID NO:3 and having catalytic activity "are essential to the operation of the claimed invention." *Id.* The procedures of making and testing sequences having 95% identity to SEQ ID NO:3 are determined to be "conventional." *Id.* Example 14 concludes that

> [t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ

> ID NO:3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.

Id. at 54-55.

Applicants' claimed invention, though directed to the nucleotide sequences encoding the proteins having DGAT activity, is structured similarly to that of the Example 14 claim. The claimed nucleotide sequences encode proteins having 95% identity to SEQ ID NO:16, with the encoded proteins having DGAT activity. Like Example 14, there is not substantial variation in the encoded proteins, because the entire genus must have 95% sequence identity to SEQ ID NO:16 and have DGAT activity. Further, Applicants provided a DGAT assay, described above, used to identify the proteins having 95% sequence identity to SEQ ID NO:16 that also have DGAT activity. Procedures for producing proteins having 95% identity to SEQ ID NO:16 are well-known in the art (*see, e.g.*, page 12, line 16 – page 13, line 35). This claim is also supported by the recent Board of Patent Appeals and Interference case (*Ex parte Kubin*, Appeal 2007-0819, May 31, 2007).

Applicants also take issue with the Examiner's statement that a further reason for claim 26 failing the written description requirement was that "neither the specification nor the prior art discloses any polypeptide that is at least 90% identical to SEQ ID NO:16 except for SEQ ID NO:16 itself." Final Office Action, at 4. First, if the prior art disclosed a sequence having 90% identity to SEQ ID NO:16, then claim 26 in its version set forth in the Response to Non-Final Office Action could possibly be obvious for claiming a nucleotide sequence of a known protein. A claim to a protein having 90% identity to SEQ ID NO:16, such as that in the canceled claims directed to amino acid sequences having 90% identity to SEQ ID NO:16, would be anticipated. As the Examiner appears to acknowledge through the absence of section 102 and 103 rejections in either the N-F Office Action or the Final Office Action, the claimed sequences at 90% identity to SEQ ID NO:16 are novel and nonobvious over the prior art, so disclosure of prior art sequences within the scope of claim 26 is not possible without anticipating the invention. Second, disclosing every variant of SEQ ID NO:16 having 90% identity thereto accomplishes nothing but creating a sequence listing of thousands of pages. The written description requirement is not so rigid. *Accord Falkner*, 448 F.3d at 1367 ("[I]t is the binding

precedent of [the Federal Circuit] that *Eli Lilly* does *not* set forth a *per se* rule that whenever a claim limitation is directed to a macromolecular sequence, the specification must always recite the gene or sequence, regardless of whether it is known in the prior art."). Having sufficient written description in a specification merely requires an application to show possession of the invention to one of ordinary skill in the art. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). By showing one sequence having 90% identity to SEQ ID NO:16 in the specification, that is SEQ ID NO:16 itself, the skilled artisan would know that every possible sequence having 90% identity thereto is readily ascertainable without reference to a sequence listing showing every possible variant of SEQ ID NO:16. The same of course is true for the even narrower claim of 95% identity to SEQ ID NO:16.

The lack of working examples and absence of disclosed structure should not affect the written description analysis. In *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357 (Fed. Cir. 2006), the Federal Circuit confirmed that

> (1) examples are not necessary to support the adequacy of a written description (2) [sic] the written description standard may be met . . . even where actual reduction to practice of an invention is absent; and (3) there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure.

Falkner, 448 F.3d at 1366 (emphasis in original). *Falkner* also noted that "a requirement that patentees recite known DNA structures, if one existed, would serve no goal of the written description requirement. It would neither enforce the quid pro quo between the patentee and the public by forcing the disclosure of new information, nor would it be necessary to demonstrate to a person of ordinary skill in the art that the patentee was in possession of the claimed invention." *Id.* at 1368. Possession of claimed invention here relates to the structure, identity to SEQ ID NO:16 (the structure of which is undisputed as evidenced by the actual sequence), correlated with function, DGAT activity.

Applicants thus respectfully request withdrawal of the rejection of claims 26 and 30-40 under 35 U.S.C. § 112, first paragraph, written description.

Enablement

Claims 26 and 29-40 were also rejected under 35 U.S.C. §112, first paragraph, for lack of enablement, since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility.

Applicants respectfully submit, for reasons cited above regarding the rejection under 35 U.S.C. § 101, that there is a specific and substantial utility for the claimed inventions.

Claims 26 and 29-40 were also rejected for lack of enablement for sequences that encode a polypeptide with at least 90% or at least 95% sequence identity to SEQ ID NO:16, for lack of guidance as to which amino acid changes could be made and still produce a functional enzyme. Because whether sequences having 90% identity to SEQ ID NO:16 is enabled is moot in light of the present amendments to claim 26, Applicants focus their response on the enablement of sequences having 95% identity to SEQ ID NO:16.

Applicants agree with the Examiner that a specification must enable one of ordinary skill in the art to make and use the claimed invention without undue experimentation. Applicants respectfully submit, however, that the Examiner's conclusion of nonenablement of sequences having 95% identity to SEQ ID NO:16 is erroneous because any experimentation needed to practice the present invention would be routine. "[A] patent specification complies with the statute even if a 'reasonable' amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be 'undue.'" *Enzo Biochem, Inc. v. Calgene, Inc.*, 118 F.3d 1362, 1371 (Fed. Cir. 1999). Factors to consider when deciding whether experimentation is undue include: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Applicants address each of the *Wands* factors below.

(1) The quantity of experimentation needed is quite low. As noted above, methods of producing nucleotide sequences are well-known in the art. The method of testing for DGAT activity cited in the specification is known in the art and has been relied on several times by other research groups for showing DGAT activity. For

example, Cases *et al.* (1998 Proc Natl Acad Sci 95:13018-13023; cited in the Information Disclosure Statement) use a modification of the procedure of Andersson *et al.* to assay DGAT activity.

(2) The specification provides sufficient direction for producing nucleotide sequences encoding proteins having 95% identity to SEQ ID NO:16 and a specific assay for DGAT activity is provided.

(3) Applicants admit that there are no working examples showing DGAT activity in the specification. The specification's lack of working examples, however, does not automatically equate to nonenablement of the claimed invention.

> A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language. That is because the patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before.

LizardTech, Inc. v. Earth Resource Mapping, Inc., 434 F.3d 1336, 1345 (Fed. Cir. 2005) (internal citation omitted).

(4) The invention is one of nucleotide sequences encoding proteins having DGAT activity. Such an invention requires some experimentation for even routine techniques.

(5) Applicants' first provisional application, US Serial No. 60/110602, filed December 2, 1998, contained partial sequences for a DGAT protein from corn (SEQ ID NO:4), rice (SEQ ID NO:12), soybean (SEQ ID NO:18) and wheat (SEQ ID NO:20). Applicants' second provisional application, US Serial No. 60/127,111, filed March 3, 1999, contained complete coding sequences for the DGAT protein from soybean (SEQ ID NO:16) and Arabidopsis (SEQ ID NO:2). Prior to filing of Applicants' first provisional application, the sequence was known for a mouse DGAT gene (Cases *et al.* 1998 Proc Natl Acad Sci 95:13018-13023; in IDS) and a putative human DGAT gene (Oelkers *et al.* 1998 J Biol Chem 273:26765-26771; in IDS). Additionally, a mutant in Arabidopsis, AS11, in the TAG1 locus was known that resulted in plants with reduced DGAT activity (Katavic *et al.* 1995 Plant Physiol 108:399-409; in IDS). The TAG1 locus was subsequently identified as encoding the DGAT gene (Zou *et al.* 1999 Plant J 19:645-653; in IDS). In determining the DGAT activity of the mouse gene, Cases *et al.* used DGAT coding sequences with or

without an N-terminal FLAG epitope (MG**DYKDDDD**G-, epitope in bold font). The DGAT activity level increased proportionately with the amount of FLAG-tagged protein (page 13020; left column), indicating that the mouse gene encodes a DGAT protein and that modification of the N-terminus did not destroy the DGAT activity.

(6) This invention is related to the biotechnical arts in a well-known pathway, triacylglycerol synthesis, and the skill level of the artisan is very high. The skilled artisan is therefore very familiar with the pathway and well versed in many methods and techniques of, for example, gene manipulation, protein synthesis, and enzyme action.

(7) Claim 26 is directed to a nucleotide sequence encoding a protein having a specified activity. It is unreasonable for Applicants to provide a cookbook recipe of how to practice the invention. Rather, Applicants have depended on the skill and experience of the skilled artisan to implement the invention using nucleotide sequences encoding enzymes having DGAT activity. Applicants expect that the skilled artisan would be aware of successful molecular biology and biochemistry methods and therefore be capable of producing the described sequences and testing these sequences for DGAT activity.

(8) The Examiner's concerns about the number of possible sequences having 95% identity to SEQ ID NO:16 are unfounded. Indeed, the number of possible claimed sequences should not itself form the basis of an enablement rejection. *See, e.g., Novozymes A/S v. Genencor Int'l, Inc.*, 446 F. Supp. 2d 297, 330 (D. Del. 2006) (noting that, with claims covering polypeptides having 95% identity to a disclosed sequence, a "large number [of possible sequences] alone is not sufficient to show a lack of enablement . . .").

Outside of factor (3), the *Wands* factors support Applicants assertion that any experimentation required to practice the present claims would be routine. "It is well established that a patent applicant is entitled to claim his invention generically when he describes it sufficiently to meet the [enablement requirement]." *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991). In *Amgen*, the court found that a generic claim covering all possible DNA sequences encoding any polypeptide having an amino acid sequence "sufficiently duplicative" of erythropoietin ("EPO") and which causes bone marrow cells to increase production of reticulocytes and red blood cells, and increases hemoglobin synthesis or iron uptake as being

nonenabled where the patentee only provided information "of how to make EPO and very few analogs." *Id.* at 1213-14. As noted in *Novozymes*, however, "[t]he problem in *Amgen* was that the claim scope covered any gene that could be used to express proteins of various sizes that had one or more of the biological properties of EPO." *Novozymes*, 446 F. Supp. 2d at 330 (emphasis added). Unlike the patentee in *Amgen*, Applicants are not claiming all nucleotide sequences encoding enzymes having DGAT activity but merely those having 95% identity to SEQ ID NO:16. Even the *Amgen* court recognized that the enablement requirement should not be extended beyond reasonableness when it noted that the disclosure at issue there might have been sufficient to enable a claim for EPO analogs similar to those described in that specification. *Amgen*, 927 F.2d at 1213 (noting that the patentee's "disclosure might well justify a generic claim encompassing these and similar analogs, but it represents inadequate support for [patentee's] desire to claim all EPO gene analogs").

Applicants' situation is similar to that in *Novozymes*. There, patentee's claim 1 read:

> A variant of a parent *Bacillus stearothermophilus* alpha-amylase, wherein the variant has an amino acid sequence which has at least 95% homology to the parent *Bacillus stearothermophilus* alpha-amylase and comprises a deletion of amino acids 179 an [sic] 180, using SEQ ID NO:3 for numbering, and wherein the variant has alpha-amylase activity.

Novozymes, 446 F. Supp. 2d at 306. The *Novozymes* court concluded that "requiring at least 95% homology with [the identified sequence] makes the variants sufficiently similar so that the enablement requirement is satisfied. By contrast to *Amgen*, the claim scope [in *Novozymes*] is limited quantitatively to similarity between protein sequences and not just to a requirement for alpha-amylase-like activity." *Novozymes*, 446 F. Supp. 2d at 300. Applicants' current claims are similarly structured. There is a quantitative limit to the similarity between SEQ ID NO:16 and other proteins in the claimed genus and all proteins having 95% identity to SEQ ID NO:16 must have DGAT activity. Thus, Applicants' claimed invention should be sufficiently enabled.

Further evidencing enablement of claim 26 is that the novel aspect of the invention is enabled in the specification. In a recent Federal Circuit case, the court

clarified that "[a]lthough the knowledge of one skilled in the art is indeed relevant [to an enablement determination], the novel aspect of an invention must be enabled in the patent." *Auto. Techs. Int'l, Inc. v. BMW of N. Am., Inc.*, 2007 U.S. App. LEXIS 21271, at*22 (Fed. Cir. Sept. 6, 2007). In the present application, the novel aspect of the invention is the sequence set forth in SEQ ID NO:16 and variants thereof. As SEQ ID NO:16 was present in the sequence listing, which is considered part of the specification as filed, the novel aspect of the invention is enabled in the specification. Whether or not the claimed sequences have DGAT activity is irrelevant to the novelty of the claimed sequences; a claim directed solely to "a nucleotide sequence encoding an amino acid sequence having 95% identity to SEQ ID NO:16" would be novel without the DGAT activity limitation, which is present for section 112 purposes only. Indeed, DGAT activity itself is not novel; as the specification notes, "[a]cyl CoA:diacylglycerol acyltransferase (DGAT, EC 2.3.1.20) uses fatty acyl CoA and diacylglycerol as substrates to catalyze the only committed step in triacylglycerol synthesis" (page 1, lines 13-15). Therefore, this knowledge can be imputed from those skilled in the art to supplement the present disclosure, as routine experimentation (a DGAT assay) provides the determination of whether a sequence having 95% identity to SEQ ID NO:16 is within the scope of the claim 26 invention. *See Invitrogen*, 429 F.3d at 1070-71 ("The scope of enablement . . . is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation.").

Applicants further note that, should the office here limit Applicants' claimed invention to only those nucleotide sequences encoding SEQ ID NO:16, Applicants' patent rights become essentially useless because the skilled artisan could simply modify one amino acid of SEQ ID NO:16 (the sequence of which is undisputedly disclosed in the specification), confirm DGAT activity by the Andersson assay (undisputedly referenced in the specification), yet be outside the scope of the Applicants' claims even though Applicants' specification disclosed the complete roadmap to working around the exceptionally narrow claims. In essence, the Examiner's scope of enablement rejection produces the absurd result of the specification enabling the skilled artisan to avoid infringement of claims covering only nucleotide sequences encoding SEQ ID NO:16, but the same specification failing to

enable the same skilled artisan to produce the same modified amino acid sequence if the claims cover sequences having 95% identity to SEQ ID NO:16.

Applicants also believe that any of the arguments presented in the enablement section should be applicable towards establishing that sufficient written description was present in the specification as filed and vice versa. As noted in *LizardTech*, "a recitation of how to make and use the invention across the full breadth of the claim is ordinarily sufficient to demonstrate that the inventor possesses the full scope of the invention, and vice versa." 434 F.3d at 1345. That the present specification supports possession (written description) of the genus of polypeptides encompassed by the present claims (see above) further evidences enablement of the present claims. All methods for generating the described polypeptide variants were standard in the art at the time of filing. Likewise, methods for testing for the required activity were described in the specification (see above). Thus, the possessed genus is enabled, almost by definition.

In view of the foregoing, Applicants respectfully request withdrawal of the Section 112, 1st paragraph, enablement rejection.

Summary

In view of the foregoing amendments and remarks, Applicants submit that this application is in condition for allowance. In order to expedite disposition of this case, the Examiner is invited to contact Applicants' representative at the telephone number below to resolve any remaining issues. Should there be a fee due which is not accounted for, please charge such fee to Deposit Account No. 501447 (Potter Anderson & Corroon LLP).

Respectfully submitted,

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